CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074872

Trade Name : ACYCLOVIR CAPSULES 200MG

Generic Name: Acyclovir Capsules 200mg

Sponsor : ESI Lederle, Inc.

Approval Date: April 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074872

APPROVAL LETTER

ANDA 74-872

APR-22-1997

ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River, NY 10965-1299

Dear Sir:

This is in reference to your abbreviated new drug application dated March 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

4-22-87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074872

FINAL PRINTED LABELING

NDC 59911-5831-2 [redacted]

ESI LEDERLE

Acyclovir Capsules

200 mg

1000 Capsules

Caution: Federal law prohibits dispensing without prescription.

[redacted]

Each capsule contains acyclovir, USP 200 mg.

Usual Dosage: See package circular for full prescribing information.

Store between 15°-25° C (59°-77° F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

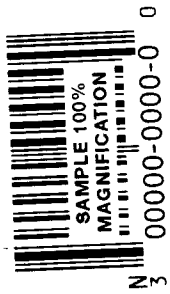
This is a bulk container not intended for household use.

ESI Lederle Inc.
Philadelphia, PA 19101

U5831-02

Control No.

Exp. Date



NDC 59911-5831-1

ESI LEDERLE

Acyclovir Capsules

200 mg

100 Capsules

Caution: Federal law prohibits dispensing without prescription.

[redacted]

Each capsule contains acyclovir, USP 200 mg.

Usual Dosage: See package circular for full prescribing information.

This is a bulk container not intended for household use.

Store between 15°-25° C (59°-77° F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

ESI Lederle Inc.
Philadelphia, PA 19101 U5831-01

Control No.

Exp. Date

Acyclovir Capsules
CI 4845

Note: It should only be for combined ingredient

LEDERLE™

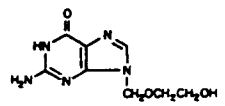
Acyclovir Capsules

DESCRIPTION

Acyclovir is an antiviral drug. Acyclovir capsules are formulated for oral administration.

Each capsule of acyclovir contains 200 mg of acyclovir and the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, and sodium starch glycolate. The capsule shells contain gelatin, titanium dioxide and black ink, which contains black iron oxide, blue #2 aluminum lake, red #40 aluminum lake, blue #1 aluminum lake and D&C yellow #10 aluminum lake.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one. It has the following structural formula:



$C_8H_{11}N_5O_3$ M.W. 225.21

Acyclovir is a white to off-white, crystalline powder with a molecular weight of 225.21, and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology

The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics

The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a reported single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg tablet was demonstrated to be bioequivalent to four acyclovir 200 mg capsules.

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy) methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE

Acyclovir capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir capsules are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies[23,24,25] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes:

Double-blind, placebo-controlled studies[26,28-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received acyclovir 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After one year of therapy, the frequency and severity of the patient's genital herpes infection should be reevaluated to assess the need for continuation of acyclovir therapy. Reevaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted

suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual reevaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections

In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox

In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented **within 24 hours** of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100°F) by the second day (19% vs. 57%). Treatment with acyclovir did not affect the antibody response to varicella-zoster virus measured 1 month and 1 year following the treatment.[35]

In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled **within 24 hours** of the onset of a typical chickenpox rash, and acyclovir was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with acyclovir reduced the median maximum number of lesions (277 vs. 386), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[36] In addition, in both studies (883 patients, ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia, and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at one month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

Diagnosis

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

CONTRAINDICATIONS

Acyclovir capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS

Acyclovir capsules are intended for oral ingestion only.

PRECAUTIONS

General

Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The recommended dosage should not be exceeded (see **Dosage and Administration**).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see **CLINICAL PHARMACOLOGY: Microbiology**).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients

Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir capsules are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for six months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for one year in humans did not show any abnormalities in structure or number of chromosomes.[28]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease.

Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions

Coadministration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day p.o.) or in rats (25 mg/kg/day s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day s.c.), there was a

statistically significant increase in postimplantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

Pregnancy

Teratogenic Effects: Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day p.o.), rabbit (50 mg/kg/day s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation Day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex

Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for one year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster

The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox

The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice

Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Treatment of Initial Genital Herpes

200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease

400 mg (two 200 mg capsules) 2 times daily for up to 12 months, followed by reevaluation. See **INDICATIONS AND USAGE** and **PRECAUTIONS** for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy

200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster

800 mg (four 200 mg capsules) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox

Children (2 years of age and older): 20 mg/kg **per dose** orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients With Acute or Chronic Renal Impairment

Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED

Acyclovir capsules for oral administration are supplied as follows:
200 mg—white, hard shell capsule imprinted "511" on the cap and "ACYCLOVIR" and "200 mg" on the body, available as:

NDC 59911-5831-1—Bottle of 100
NDC 59911-5831-3—Bottle of 100 with CRC
NDC 59911-5831-2—Bottle of 1000

CODE INSERTED HERE

Caution: Federal law prohibits dispensing without prescription.

DISPENSE IN A TIGHT, LIGHT-RESISTANT CONTAINER WITH A CHILD-RESISTANT CLOSURE. PROTECT FROM LIGHT AND MOISTURE.

STORE BETWEEN 15°-25°C (59°-77°F).

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ESI Lederle Inc.
Philadelphia, PA 19101

CI 4845 Issued February 6, 1997 Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074872

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA **74-872**

3. NAME AND ADDRESS OF APPLICANT
ESI Lederle, Inc.
401 North Middletown Road
Pearl River, NY 10965-1299

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Burroughs Wellcome's ZOVIRAX®
(NDA 18-828). Patent certification and exclusivity statement are provided (pp. 007-008).

Final approval date is January 25, 1985.

U.S. Patent No. 4,199,574 expires April 22, 1997

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Acyclovir Capsules

7. PROPRIETARY NAME
Zovirax®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		**FDA**	
Orig. submission	3/27/96	Acknowledgment letter	2/16/96
		CSO review	3/29/96
		Labeling review	10/10/96
		Bioequivalency	9/30/96
		Deficiency letter	11/04/96
Amendment (major)	11/26/96	Method validation	12/13/96
		Labeling review	1/07/97

This review covers submission dated 11/26/96.

10. PHARMACOLOGICAL CATEGORY
Indicated in the treatment of initial episodes and the management of recurrent episodes of genital herpes, also indicated for the treatment of herpes zoster (shingles) and chickenpox (valicella).

11. Rx or OTC
℞

12. RELATED DMF(s)
DMF (b)4 - Confidential Business

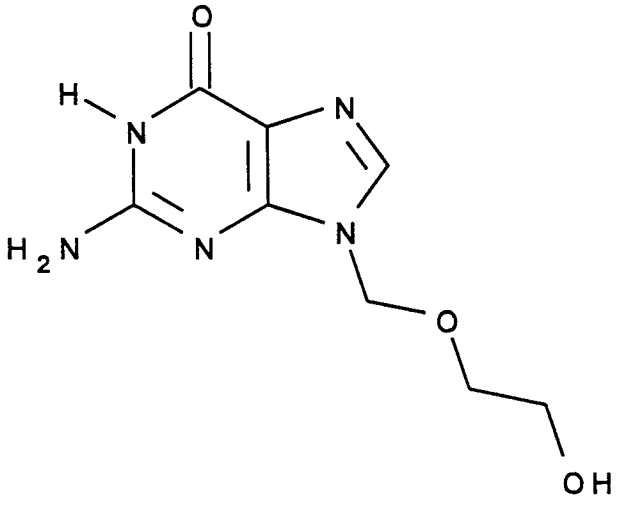
(b)4 - Confidential Business

13. DOSAGE FORM
Capsules **(HARD GELATIN)**

14. STRENGTH
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
$C_8H_{11}N_5O_3$; M.W. = 225.21



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

Drug substance is an official USP 23 item. ***Drug product is not an official USP 23 item.***

16. RECORDS AND REPORTS None

17. COMMENTS

a. Labeling is satisfactory, dated 1/17/97
b. Bio is satisfactory, letter issued 10/3/96
c. DMF (b)4 - is satisfactory, dated 1/31/97
d. Methods validation for drug product conducted by the Northeast Regional Laboratory (NY) has been found suitable for regulatory analysis, dated 12/23/96
e. Drug Substance does not require Methods validation
f. Establishment evaluation found satisfactory, dated 7/19/96.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER: Raymond Brown

DATE COMPLETED: February 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074872

BIOEQUIVALENCE REVIEW(S)

ANDA 74-872

OCT - 3 1996

ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River NY 10965-1299

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The testing should be conducted in 900 mL Purified Water using USP 23 Apparatus I (Basket) at 100 R.P.M. The test product should meet the following specifications:

   Not less than (b)(4) of the labeled amount of acyclovir is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 30 1996

Acyclovir Capsule, 200 mg
ANDA #74-872
Reviewer: S.P. Shrivastava
WP #74872SDW.396

ESI-Lederle, Inc.
Pearl River, NY
Submitted:
March 27, 1996

REVIEW OF TWO BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

I. BACKGROUND

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside analog with *in vivo* and *in vitro* inhibitory activity against (in decreasing order) herpes simplex types 1 and 2 viruses, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Acyclovir is converted by enzymes present in virus-infected cells into an active form, acyclovir triphosphate, which interrupts viral DNA replication. Acyclovir capsules and suspension are indicated for treatment of initial episodes and management of recurrent herpes simplex virus genitalis in certain patients. The capsule, suspension, and tablet dosage forms are indicated for treatment of acute herpes zoster and chicken pox.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered I.V. to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

Acyclovir is marketed as Zovirax^{R} (Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 400 mg and 800 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

In this submission, the firm has submitted two bioequivalence studies, and dissolution testing data.

II. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # 95-098 MA

This randomized, single-dose, two-way crossover study was conducted with 30 healthy male volunteers in accordance with the Protocol. Six subjects, #6, 13, 15, 25, 27, and 30 were found positive in drug screen prior to Period 2 of the study. Four subjects, Sub 6, 15, 27, and 30 returned two weeks later, and Sub #13 and 25 did not return to complete phase two of the study. Thus 28 subjects completed the study.

In each period, subjects received a single 200 mg dose of either Lederle's acyclovir capsules or BW's Zovirax[R] Capsules following an overnight fast. There was a one-week wash-out period between treatments. Blood samples were collected pre-dose and for 24 hours after each dose. Plasma concentrations of acyclovir was measured by a fully validated HPLC procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference treatments.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two acyclovir formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study under fasting conditions.

4. Study sites

Clinical study:
Analytical study: (b)4 - Confidential Business

5. Study dates:

Clinical study: 12/2/95-12/10/95 (All subjects Except Subject #6, 15, 27, and 30)
12/2/95-12/24/95 (Make-up group, Subject #6, 15, 27, and 30)
Analytical study: 12/14/95-1/12/96
Storage Time: 41 Days

6. Investigators:

Principal Investig
Analytical Chemi
Study Monitor - (b)4 - Confidential Business

A. Test: 200 mg Acyclovir Capsules (Lederle, Lot #93265-0100);
Exp. Date - 10/30/96. (b)4 - Confidential Potency - 99.5%.

B. Reference: 200 mg Zovirax[R] Capsules (Burroughs Wellcome, Lot #5P2223);
Exp. Date 6/30/96. Potency - 97.5%.

7. Dosing: All doses were administered with 180 ml of room temperature water following an overnight fast.

8. Subjects: The 30 subjects who entered in this study were normal healthy male volunteers aged 18-40 years, weighing at least 60 kg, and within 10% of their ideal body weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection

of the subjects.

Twenty-eight subjects completed both arms of the study. Subjects #13 and 25 failed to return to Period 2 of the study. In addition, Subjects #6, 15, 27 and, 30 were found positive in drug screen prior to dosing for Period 2, and they were dosed one week later. The reviewer analyzed the data with and without subject #6, 15, 27 and 30.

9. Food and fluid intake: Standard lunch was served 5 hours post-dose and dinner was served as scheduled on each day of drug administration. The drug products were administered with 180 mL of tap water. Water was allowed *ad lib.* one hour pre-dose and 2 hours post-dose.

10. Washout period: One week.

11. Blood samples: In each period, 10 mL of blood samples were collected in Vacutainers at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours. Plasma was separated and all plasma samples were stored frozen at -20°C until ready for analysis.

12. Subject safety monitoring: Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.

13. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for AUC_{0-t} , AUC0-∞ and C_{max}.

B. Limited-Food Study

1. Protocol # 95-099 MA

2. Study design: Randomized, single-dose, three-way crossover study under fasting/non-fasting conditions.

3. Study Sites and Investigators: Site, Study Monitor, and Analytical Chemist same as in Fasting Study. Principal Investigator for this study was [redacted](b)4 -[redacted]

4. Study dates: Clinical study - 12/1/95-12/16/95
   Analytical study - 12/27/95-1/9/96
   Max. Storage Period: 40 Days

5. Treatments:

A. Test: 200 mg Acyclovir Capsules (Lederle, Lot #93265-0100) under non-fasting conditions, Exp. Date - 10/30/96.

B. Reference: 200 mg Zovirax^{R} Capsules (Burroughs Wellcome, Lot #5P2223) under non-fasting conditions; Exp. Date - 6/30/96.

C. Test: 200 mg Acyclovir Capsules (Lederle, Lot #93265-0100) under fasting conditions.

6. Dosing: All doses were administered with 180 mL of water at room temperature following an overnight fast or within 5 minutes after consuming the breakfast depending on the dosing schedule.

7. Subjects: Twenty-one subjects entered the study and 19 completed the three phases. Subjects #10 did not check-in for Period 2, and Subject 17 was dropped due to concurrent illness prior to Period 3 dosing, respectively.

The subjects screened were normal healthy male volunteers aged 19-40 years, and were within 10% of their ideal body weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

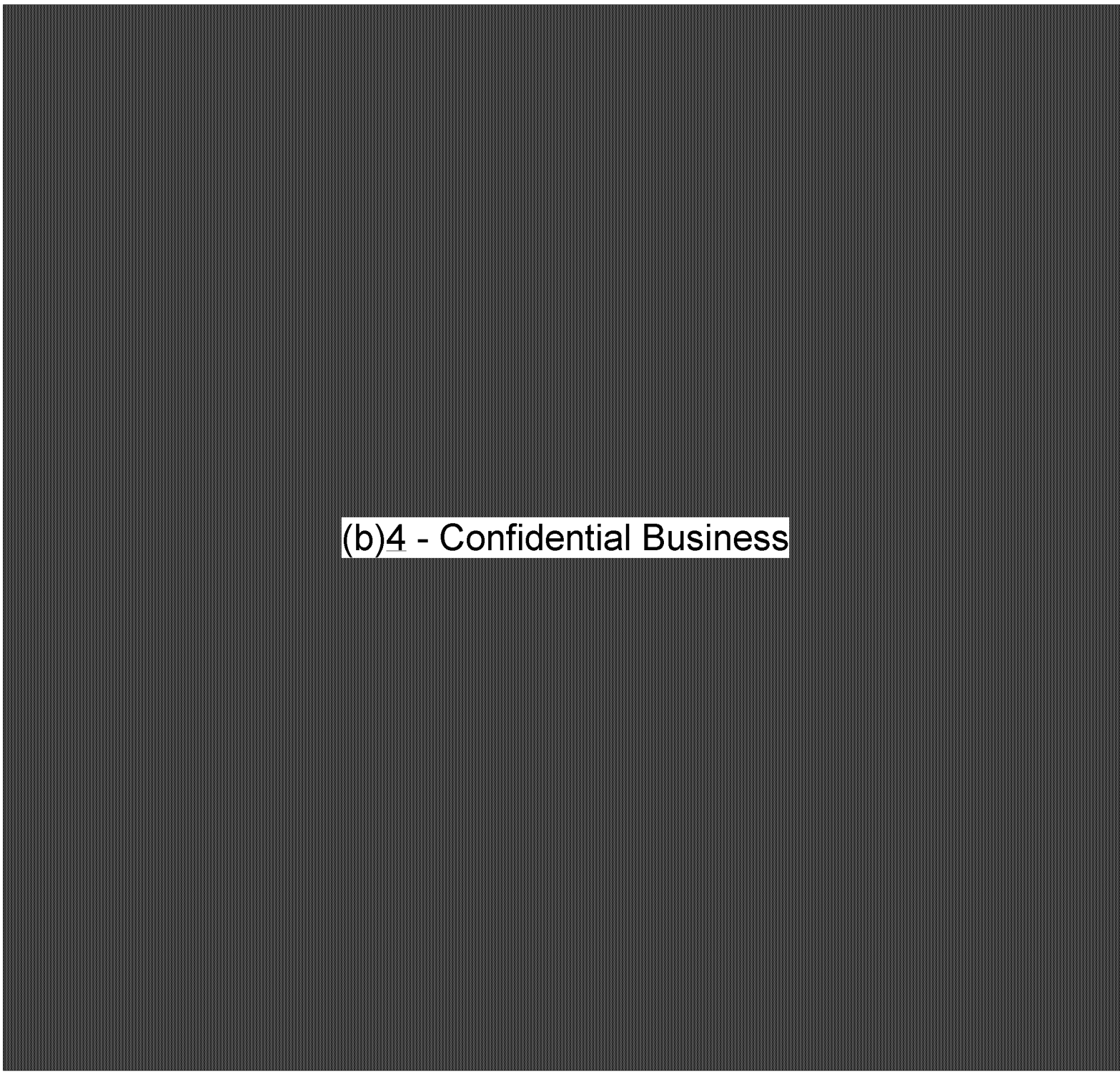
8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 180 mL of tap water. Water was allowed *ad lib.* one hour pre-dose and 2 hours post-dose.

9. Wash-out period: One week.

10. Blood samples: Same as in the fasting study.

III. VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

(b)4 - Confidential Business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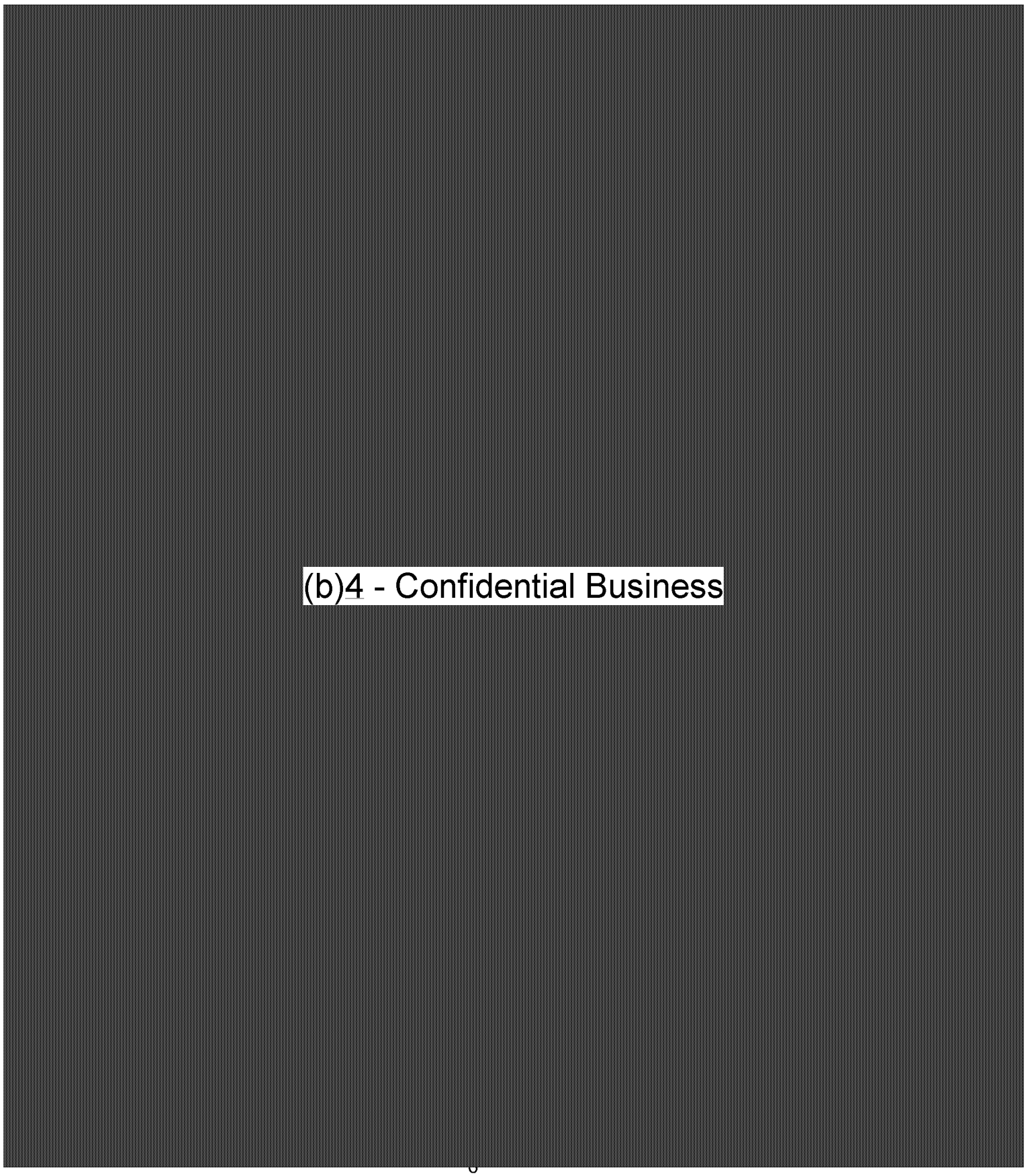
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IV. RESULTS

A. Single-Dose Fasting Study

1. **Blood/Plasma Drug Concentration:** During Period 2, Subjects #6, 15, 27, and 30 were found positive in drug screen, therefore, they were dosed one week later. These subjects should not belong to the same study period. So, they were analyzed in three ways by the reviewer.

   (a) 28 Subjects in two treatments, three periods (Table 6, Attachment 1).
   (b) 28 Subjects in two treatments, two periods (Table 9).
   (c) 24 Subjects, two periods (excluding Subjects #6, 15, 27, and 30; Tables 12, Attachment 2).

2. **Pharmacokinetic Parameters**: Mean PK parameters for 28 subjects three periods, 28 subjects two periods, and 24 subjects two periods (without Subject #6, 15, 27, and 30) are given in Tables 7-8, 10-11 and 13-14, respectively. Individual data submitted for all 28 subjects are given in Attachments 3-4. Since the correct analysis is to treat the 28 subjects in three periods, following summary statements mainly apply to those results from 28 subjects (Tables 6-8).

- The 90% CI for LAUCs and LC_{max} are within 80-125% when all 28 subjects are included (Tables 8, 11). However, when Subjects #6, 15, 27 and 30 are excluded, LC_{max} does not meet the 90% CI criteria (Table 14). LC_{max} for the test product is 10% lower than the reference drug.
- Individual Test/Reference ratios for AUC_{0-t} ranged between [redacted] with an average of 1.08 and CV of 53%.
- Individual Test/Reference ratios for AUC_{0-inf} ranged between [redacted] with an average of 1.06 and CV of 48%.
- Individual Test/Reference ratios for C_{max} ranged between [redacted] with an average of 1.00 and CV of 45%.
- Individual Test/Reference ratios for T_{max} ranged between [redacted] with an average of 1.32 and CV of 62%.
- The ratios of AUC_{0-t}/AUC_{0-inf} ranged between [redacted] with an average of 0.95 and CV of 2.6%.
- Individual PK parameters and summary data submitted by the firm are given in

Attachments-3-4.

3. **Adverse Reaction:** No serious or unexpected adverse reactions were reported.

Sign/Symptom	**Test**	**Reference**	**Drug Related**
Headache	2	1	Probable/Possible
Light-Headed	0	1	Probable/Possible
Vomiting	0	1	Possible

The *in vivo* fasting study is acceptable.

TABLE 6. PLASMA CONCENTRATION OF ACYCLOVIR IN FASTING SUBJECTS (N=28, THREE PERIOD)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	21.60	25.63	17.17	25.15	1.26
0.67	176.07	101.37	162.22	78.10	1.09
1	262.25	108.66	281.88	116.81	0.93
1.33	300.40	109.20	337.39	142.85	0.89
1.67	312.75	112.57	369.57	175.80	0.85
2	312.00	124.85	354.57	171.39	0.88
2.5	302.16	132.27	318.84	153.92	0.95
3	273.57	130.94	278.71	140.68	0.98
4	217.96	112.57	219.78	123.92	0.99
5	177.88	96.69	175.92	105.46	1.01
6	136.29	78.59	135.89	79.58	1.00
8	85.82	44.62	86.89	47.19	0.99
10	52.61	23.73	55.63	28.57	0.95
12	35.41	14.40	35.88	16.72	0.99
16	15.76	8.69	16.59	8.56	0.95
20	6.82	7.21	7.03	7.39	0.97
24	3.26	5.30	2.23	4.91	1.47

1=TEST, 2=REFERENCE

TABLE 7. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=28, THREE PERIOD)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1985.97	791.53	2059.62	891.50	0.96
AUCT	1904.21	791.77	1973.62	896.35	0.96
CMAX	361.75	133.43	400.88	166.99	0.90
KE	0.17	0.05	0.17	0.04	1.03
LAUCI	1849.27	0.38	1885.80	0.43	0.98
LAUCT	1762.18	0.40	1788.82	0.46	0.99
LCMAX	338.86	0.37	366.98	0.44	0.92
THALF	4.42	1.56	4.41	1.23	1.00
TMAX	1.90	0.89	1.59	0.65	1.19

1=TEST, 2=REFERENCE

TABLE 8. LSMEANS AND 90% CONFIDENCE INTERVALS (N=28, THREE PERIOD)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	2123.02	2165.04	82.34	113.78
AUCT	2050.56	2086.18	81.96	114.62
CMAX	392.71	424.29	77.93	107.18
LAUCI	2038.82	2029.24	85.15	118.55
LAUCT	1967.07	1943.04	85.11	120.41
LCMAX	379.25	399.37	80.04	112.66

1=TEST, 2=REFERENCE

TABLE 9. PLASMA CONCENTRATION OF ACYCLOVIR IN FASTING SUBJECTS (N=28)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	21.60	25.63	17.17	25.15	1.26
0.67	176.07	101.37	162.22	78.10	1.09
1	262.25	108.66	281.88	116.81	0.93
1.33	300.40	109.20	337.39	142.85	0.89
1.67	312.75	112.57	369.57	175.80	0.85
2	312.00	124.85	354.57	171.39	0.88
2.5	302.16	132.27	318.84	153.92	0.95
3	273.57	130.94	278.71	140.68	0.98
4	217.96	112.57	219.78	123.92	0.99
5	177.88	96.69	175.92	105.46	1.01
6	136.29	78.59	135.89	79.58	1.00
8	85.82	44.62	86.89	47.19	0.99
10	52.61	23.73	55.63	28.57	0.95
12	35.41	14.40	35.88	16.72	0.99
16	15.76	8.69	16.59	8.56	0.95
20	6.82	7.21	7.03	7.39	0.97
24	3.26	5.30	2.23	4.91	1.47

1=TEST, 2=REFERENCE

TABLE 10. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=28)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1985.97	791.53	2059.62	891.50	0.96
AUCT	1904.21	791.77	1973.62	896.35	0.96
CMAX	361.75	133.43	400.88	166.99	0.90
KE	0.17	0.05	0.17	0.04	1.03
LAUCI	1849.27	0.38	1885.80	0.43	0.98
LAUCT	1762.18	0.40	1788.82	0.46	0.99
LCMAX	338.86	0.37	366.98	0.44	0.92
THALF	4.42	1.56	4.41	1.23	1.00
TMAX	1.90	0.89	1.59	0.65	1.19

1=TEST, 2=REFERENCE

TABLE 11. LSMEANS AND 90% CONFIDENCE INTERVALS (N=28)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	1985.97	2059.62	83.96	108.89
AUCT	1904.21	1973.62	83.43	109.54
CMAX	361.75	400.88	78.40	102.08
LAUCI	1849.27	1885.80	86.25	111.49
LAUCT	1762.18	1788.82	86.03	112.81
LCMAX	338.86	366.98	80.75	105.59

1=TEST, 2=REFERENCE

TABLE 12. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS (N=24)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	21.71	26.18	16.00	24.90	1.36
0.67	170.14	87.27	162.77	76.03	1.05
1	259.58	99.25	281.25	112.29	0.92
1.33	300.57	110.12	332.12	132.83	0.91
1.67	314.90	117.67	368.87	172.31	0.85
2	314.18	132.84	352.07	167.90	0.89
2.5	303.07	141.57	317.76	153.98	0.95
3	271.72	139.53	277.29	139.90	0.98
4	212.20	117.11	220.16	125.39	0.96
5	173.33	101.66	175.56	106.65	0.99
6	134.15	83.82	136.35	80.48	0.98
8	85.15	47.82	87.87	48.40	0.97
10	51.80	25.24	56.75	29.37	0.91
12	35.25	15.24	36.37	17.06	0.97
16	15.68	8.48	17.14	8.35	0.91
20	6.24	7.21	7.03	7.39	0.89
24	2.88	5.15	2.10	4.85	1.37

1=TEST, 2=REFERENCE

TABLE 13. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=24)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1962.13	841.23	2063.62	890.05	0.95
AUCT	1881.41	842.60	1976.08	893.75	0.95
CMAX	361.55	139.44	401.42	160.20	0.90
KE	0.17	0.05	0.17	0.04	1.04
LAUCI	1810.48	0.40	1901.88	0.41	0.95
LAUCT	1723.57	0.42	1805.40	0.43	0.95
LCMAX	336.66	0.39	373.70	0.38	0.90
THALF	4.38	1.54	4.42	1.21	0.99
TMAX	1.81	0.80	1.60	0.67	1.13

1=TEST, 2=REFERENCE

TABLE 14. LSMEANS AND 90% CONFIDENCE INTERVALS (N=24)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	1967.54	2072.09	81.02	108.88
AUCT	1886.67	1984.54	80.50	109.63
CMAX	361.24	400.93	77.20	103.00
LAUCI	1819.08	1908.24	83.50	108.83
LAUCT	1732.36	1811.94	83.28	109.76
LCMAX	336.84	373.26	78.76	103.40

1=TEST, 2=REFERENCE

B. Limited Food Study

A total of 21 subjects participated in the study, and 19 completed the study successfully. Two subjects, Subject #10 did not check-in for Period 2, and Subject #17 was dropped due to concurrent illness.

1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given in Tables 15-16 and Attachment-5. Test Fed/Reference Fed ratios during 1-24 hours are 0.41-1.22.

2. Pharmacokinetic Parameters

- Average pharmacokinetic parameters and test/reference (food) ratios are given in Tables 17-20.
- The ratios of average test/reference (food) for AUCs and C_{max} are within 0.8-1.2 as required (Tables 18).
- ANOVA analysis showed no significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.
- Individual PK parameters are given in Attachments 6-8.
- Food appears to decrease the AUCs, C_{max}, and T_{half}, and increase T_{max}.

3. **Adverse Reaction**: No difference between test fed and reference fed were found.

Sign/Symptom	Test-Fed	Reference-Fed	Test-Fasting	Drug Related
Headache	2	2	3	Probable
Vomiting	0	1	0	Possible

The *in vivo* non-fasting study is acceptable.

TABLE 15. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	0.00	0.00	0.00	0.00	31.99	42.53
0.67	5.25	10.53	22.57	47.74	170.44	120.05
1	35.57	39.56	87.10	96.59	283.54	136.18
1.33	105.22	104.55	175.30	105.46	362.23	171.60
1.67	191.89	148.40	265.38	107.79	391.03	195.21
2	252.00	161.48	313.57	113.63	391.83	202.74
2.5	295.28	126.83	342.84	101.83	349.66	194.44
3	315.87	82.83	326.68	93.75	312.96	193.72
4	293.23	78.18	262.45	77.89	254.25	156.43
5	236.99	84.87	205.66	62.56	195.74	129.75
6	175.92	64.14	152.99	49.62	147.05	100.26
8	101.85	38.70	91.29	30.88	92.45	54.82
10	61.64	23.55	55.51	19.56	58.62	32.70
12	39.98	16.96	36.47	13.08	39.02	20.89
16	19.29	9.44	18.85	8.40	20.37	11.10
20	8.63	8.77	7.08	9.08	10.78	8.34
24	4.27	6.59	4.98	6.84	5.57	8.01

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 16. RATIO OF TEST/REFERENCE MEAN PLASMA ACYCLOVIR LEVELS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	.	0.00	0.00
0.67	0.23	0.03	0.13
1	0.41	0.13	0.31
1.33	0.60	0.29	0.48
1.67	0.72	0.49	0.68
2	0.80	0.64	0.80
2.5	0.86	0.84	0.98
3	0.97	1.01	1.04
4	1.12	1.15	1.03
5	1.15	1.21	1.05
6	1.15	1.20	1.04
8	1.12	1.10	0.99
10	1.11	1.05	0.95
12	1.10	1.02	0.93
16	1.02	0.95	0.93
20	1.22	0.80	0.66
24	0.86	0.77	0.90

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 17. TEST MEAN/REFERENCE MEAN (ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	2030.75	598.10	2025.40	536.71	2377.89	1089.06
AUCT	1944.28	582.95	1926.74	515.80	2194.16	1123.83
CMAX	361.19	105.67	375.37	87.60	432.18	206.31
KE	0.17	0.05	0.16	0.06	0.16	0.06
LAUCI	1961.33	0.26	1954.47	0.28	2164.66	0.45
LAUCT	1875.87	0.26	1857.74	0.28	1938.25	0.52
LCMAX	348.66	0.26	365.33	0.24	375.42	0.61
THALF	4.44	1.41	4.82	1.67	5.05	2.08
TMAX	2.83	0.83	2.49	0.82	1.80	0.85

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 18. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.00	0.85	0.85
AUCT	1.01	0.89	0.88
CMAX	0.96	0.84	0.87
KE	1.04	1.07	1.03
LAUCI	1.00	0.91	0.90
LAUCT	1.01	0.97	0.96
LCMAX	0.95	0.93	0.97
THALF	0.92	0.88	0.95
TMAX	1.14	1.58	1.39

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 19. LSMEANS AND 90% CONFIDENCE INTERVALS
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LSMEAN3	LOWCI12	UPPCI12	LOWCI13
PARAMETER						
AUCI	2051.25	2045.14	2423.13	85.39	115.21	72.07
AUCT	1957.59	1945.88	2207.47	83.86	117.35	73.92
CMAX	359.92	377.35	430.91	77.04	113.71	67.47
LAUCI	1977.88	1978.61	2204.63	87.62	114.04	78.64
LAUCT	1885.52	1882.92	1948.21	85.27	117.60	82.41
LCMAX	346.97	368.70	373.59	76.24	116.16	75.24

TABLE 20. LSMEANS AND 90% CONFIDENCE INTERVALS
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	UPPCI13	LOWCI23	UPPCI23
PARAMETER			
AUCI	97.24	71.81	96.99
AUCT	103.44	73.39	102.91
CMAX	99.58	71.51	103.63
LAUCI	102.35	78.67	102.39
LAUCT	113.66	82.30	113.50
LCMAX	114.64	79.95	121.82

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

V. FORMULATION

Table 21. shows the composition of the test products, 200 mg Acyclovir Capsules by Lederle.

The ingredients used in the test product are within the IIG (1996) limits. The executed batch size was [redacted] (b)4 - Confidential

[NOT FOR RELEASE UNDER F.O.I.]

Table 21. Composition of Lederle's Acyclovir Capsules

Ingredient	Test	Reference
Acyclovir, USP	200.000	200.000
Silicon Dioxide Colloidal, NF	[redacted]	
Cellulose Microcrystalline, NF		
Magnesium Stearate, NF		
Povidone USP (K30)		
Sodium Starch Glycolate, NF		
Purified Water[1], USP		
Ink Black		
Lactose		
Sodium Lauryl Sulfate		
Starch, Corn		
Unspecified ingredient		
Dye FDC Blue #2		
Titanium Dioxide		
Gelatin		

(b)4 - Confidential Business

[1] Used in the manufacturing process, but does not appear in the final product.

[2] PNG = Potency and grade not given.

VI. *IN VITRO* RESULTS (DISSOLUTION)

The capsules meet the dissolution requirement of Q=NLT (b)4 in 30 minutes (Table 22).

TABLE 22. *In Vitro* Dissolution Testing

Method: Used FDA method. USP method not available.
Apparatus I (Basket) **RPM: 100** **No. of Units: 12**
Medium: water **Volume:** 900 mL
Reference Drug: Zovirax® **Manufacturer:** Burroughs-Wellcome
Assay Methodology (b)4 -

Sampling Time	Test Product			Reference Product		
(Minutes)	Mean % Dissol	Range	CV	Mean % Dissol	Range	CV
	Lot #93265-0100		Strength 200 mg		Lot # 5P2223	
10	76	(b)4 - ıfidel ısine	20.5	61	(b)4 - nfider usines	22.2
20	86		11.5	81		5.0
30	92		6.3	90		6.8
40	95		4.0	97		7.3

*Dissolution results are acceptable according to the Acceptance Table on page 1793 of USP XXIII (1995).

VII. COMMENTS

1.

2. (b)4 - Confidential Business

VIII. RECOMMENDATIONS

1. The *in vivo* bioequivalence studies, under fasting and non-fasting conditions, conducted by ESI-Lederle on its acyclovir capsules, 200 mg strength, Lot #93265-0100, comparing it to Burroughs-Wellcome's Zovirax^{R}, 200 mg Capsules, Lot #5P2223, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that ESI-Lederle's acyclovir, 200 mg capsules, are bioequivalent to the reference product, Zovirax^{R} 200 mg capsules, manufactured by Burroughs-Wellcome.

2. The dissolution testing conducted by ESI-Lederle, on its acyclovir, 200 mg capsules, Lot #93265-0100, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The testing should be conducted in 900 mL Purified Water using USP XXIII Apparatus I (Basket) at 100 R.P.M. The test product should meet the following specifications:

   Not less than (b)4 (Q) of the labeled amount of acyclovir is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its acyclovir 200 mg capsules, and the application is acceptable.

The firm should be informed of the comments and recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALE
FT INITIALE /S/ te 9/30/1996

Concur: 9/30/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Attachments-8

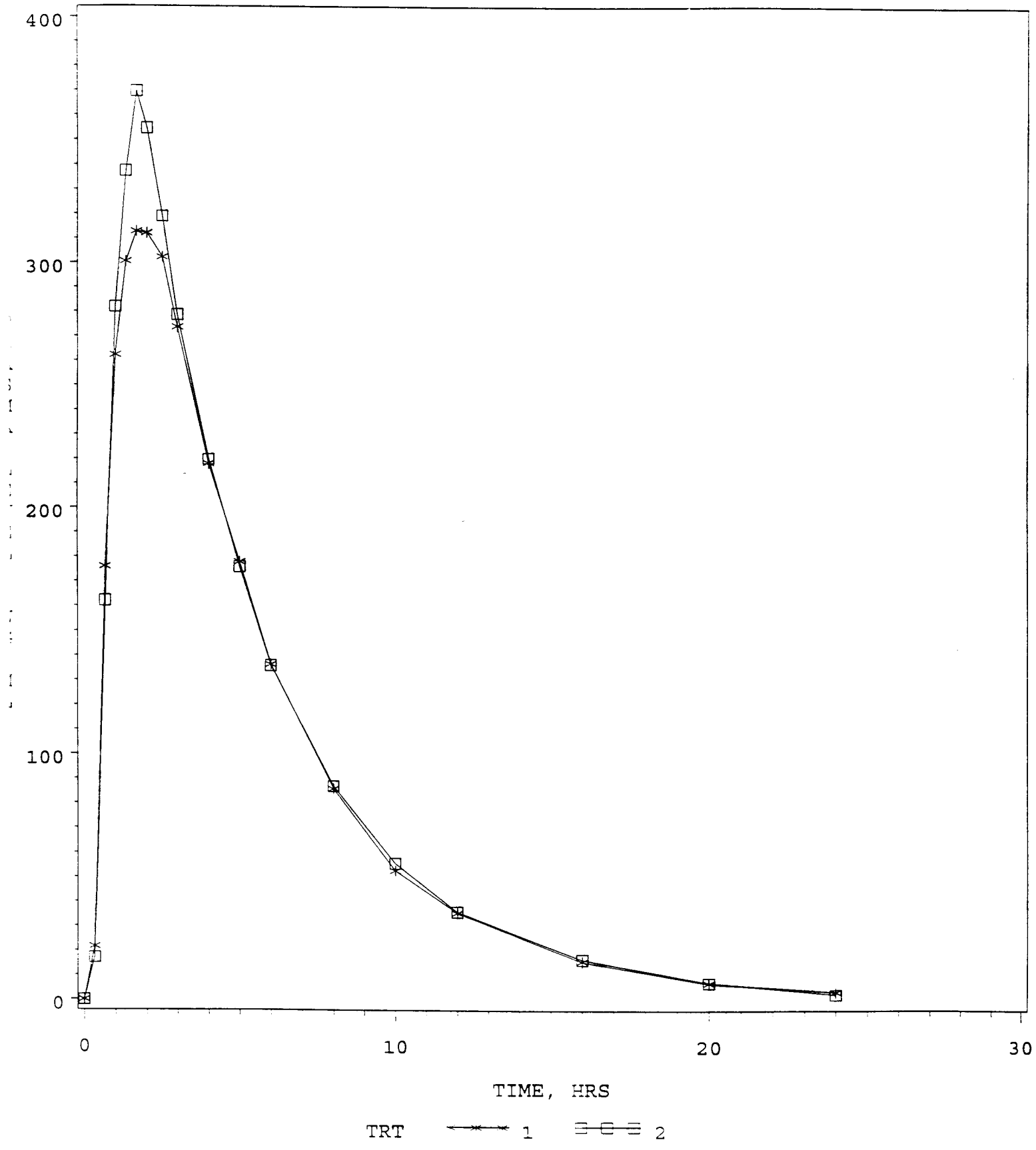
SPS/sps/7-24-96/74872SDW.396

cc: ANDA #74872 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

Attachment - 1

FIG P-1. ACYCLOVIR CAPSULES: PLASMA LEVELS

ACYCLOVIRCAPSULES, 200 MG, ANDA #74-872
UNDER FASTING CONDITIONS
DOSE=1 X 200 MG

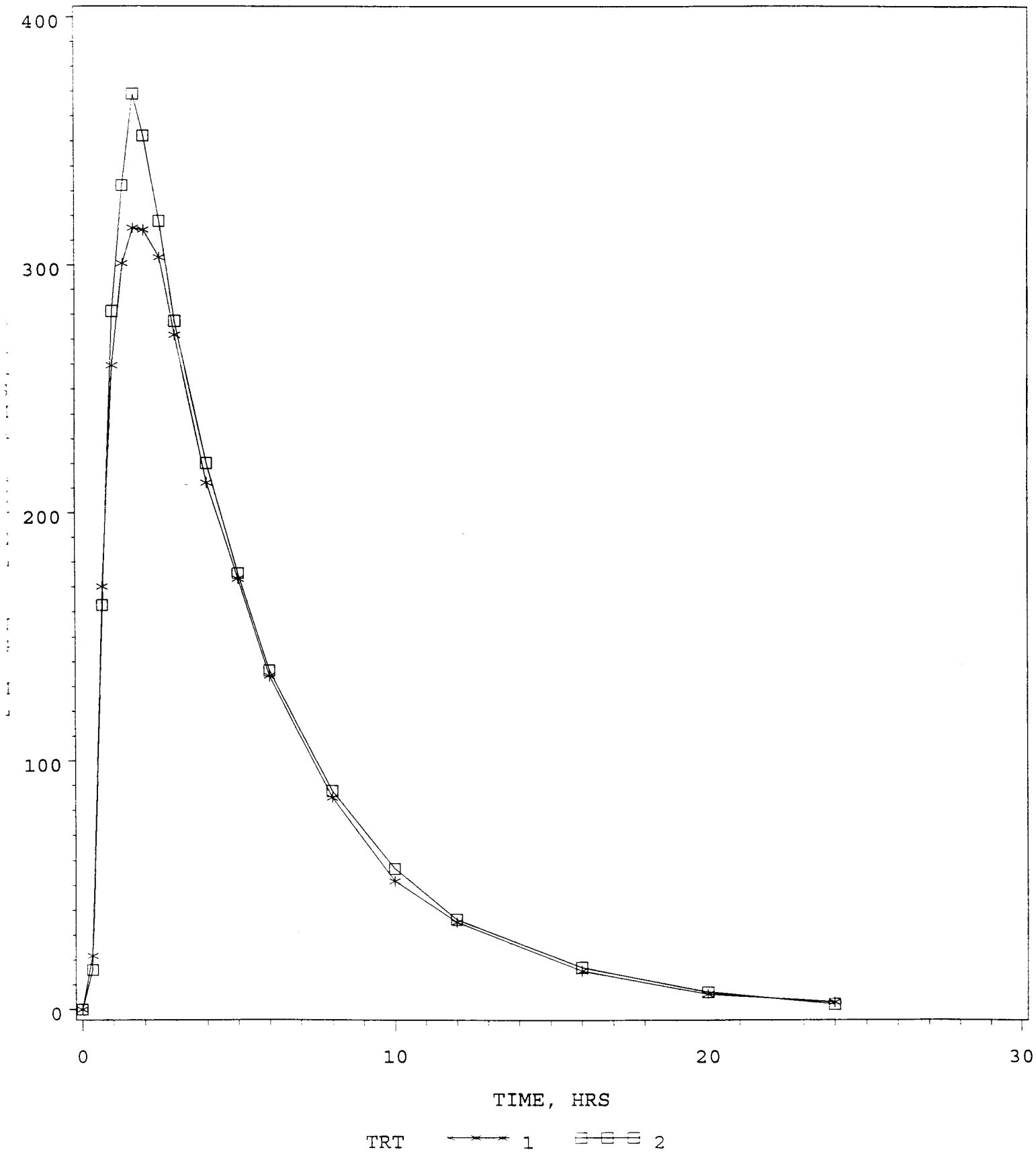


1=TEST PRODUCT(ESI-LEDERLE) 2=REFERENCE PRODUCT(BURROUGHS-WELLCOME)

Attachment-2

IG P-1. ACYCLOVIR CAPSULES: PLASMA LEVELS (N=24)

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-872
UNDER FASTING CONDITIONS
DOSE=1 X 200 MG



1=TEST PRODUCT(ESI-LEDERLE) 2=REFERENCE PRODUCT(BURROUGHS-WELLCOME)

Attachment- 3

Wyeth-Ayerst Laboratories
ACyclovir Protocol 95-098-MA
Harris Laboratories Project 17962

Table 4

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Acyclovir 200 mg Capsule (ESI Lederle)

Subject Number	Treatment Sequence	Study Period	Parameters					Log-Parameters	
			Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel T 1/2el 1/hr hr	LN(Cmax)	LN[AUC(0-t)] LN[AUC(0-inf)]
1	BA	2	361.8	1.90	1904.2	1986.0	0.1733 4.42	5.826	7.474 7.523
2	AB	1	133.9	0.89	791.8	791.5	0.0505 13.72	4.896	6.674 6.673
3	AB	1	36.9	46.74	149.6	149.6	0.1276 35.19	3.607	5.008 5.009
4	BA	2	25.2	0.17	149.6	149.6	0.0095 0.29	3.227	5.008 5.072
5	BA	2	28.0	28.00	28.0	28.0	0.0000 28.00	3.332	3.332 28.000
6	AB	1	151.3	0.67	892.1	958.4	0.0887 2.69	5.019	6.794 6.865
7	AB	1	701.1	4.00	4214.3	4279.9	0.2576 7.82	6.553	8.346 8.362
8	BA	2							
9	AB	1							
10	BA	2							
11	BA	2							
12	AB	1							
13	AB	1							
14	BA	2							
15	AB	1							
16	BA	2							
17	BA	2							
18	AB	1							
19	BA	2							
20	AB	1							
21	BA	2							
22	AB	1							
23	AB	1							
24	BA	2							
25	AB	1							
26	BA	2							
27	BA	2							
28	AB	1							
29	BA	2							
30	AB	1							
	BA								
Mean			361.8	1.90	1904.2	1986.0	0.1733 4.42	5.826	7.474 7.523
S.D.			133.9	0.89	791.8	791.5	0.0505 1.56	0.371	0.398 0.381
C.V.(%)			36.9	46.74	149.6	149.6	0.1276 35.19	6.374	5.326 5.069
S.E.M.			25.2	0.17	149.6	149.6	0.0095 0.29	0.070	0.075 0.072
N			28.0	28.00	28.0	28.0	0.0000 28.00	28.000	28.000 28.000
Minimum			151.3	0.67	892.1	958.4	0.0887 2.69	5.019	6.794 6.865
Maximum			701.1	4.00	4214.3	4279.9	0.2576 7.82	6.553	8.346 8.362

(b)4 - Confidential Business

Wyeth-Ayerst Laboratories
Acyclovir Protocol 95-098-MA
Matris Laboratories Project 17962

Table 5

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Zovirax(R) 200 mg Capsule (Burroughs Wellcome Co.)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	BA	1	[redacted]								
2	AB	2									
3	AB	1									
4	BA	1									
5	BA	1									
6	AB	2									
7	BA	1									
8	AB	2									
9	AB	2									
10	BA	1									
11	BA	1									
12	AB	2									
14	AB	2									
15	AB	2									
16	BA	1									
17	BA	1									
18	AB	2									
19	BA	1									
20	AB	2									
21	BA	1									
22	AB	2									
23	BA	1									
24	AB	2									
26	BA	1									
27	AB	2									
28	BA	1									
29	AB	2									
30	BA	1									
Mean			400.9	1.59	1973.6	2059.6	0.1678	4.41	5.905	7.489	7.542
S.D.			167.0	0.65	896.4	891.5	0.0413	1.23	0.443	0.457	0.431
C.V.(%)			41.7	41.11	45.4	43.3	24.6074	27.80	7.499	6.106	5.711
S.E.M.			31.6	0.12	169.4	168.5	0.0078	0.23	0.084	0.086	0.081
N			28.0	28.00	28.0	28.0	28.0000	28.00	28.000	28.000	28.000
Minimum			110.6	0.67	649.2	743.1	0.0908	2.78	4.706	6.476	6.611
Maximum			805.8	4.00	4092.6	4177.1	0.2491	7.63	6.692	8.317	8.337

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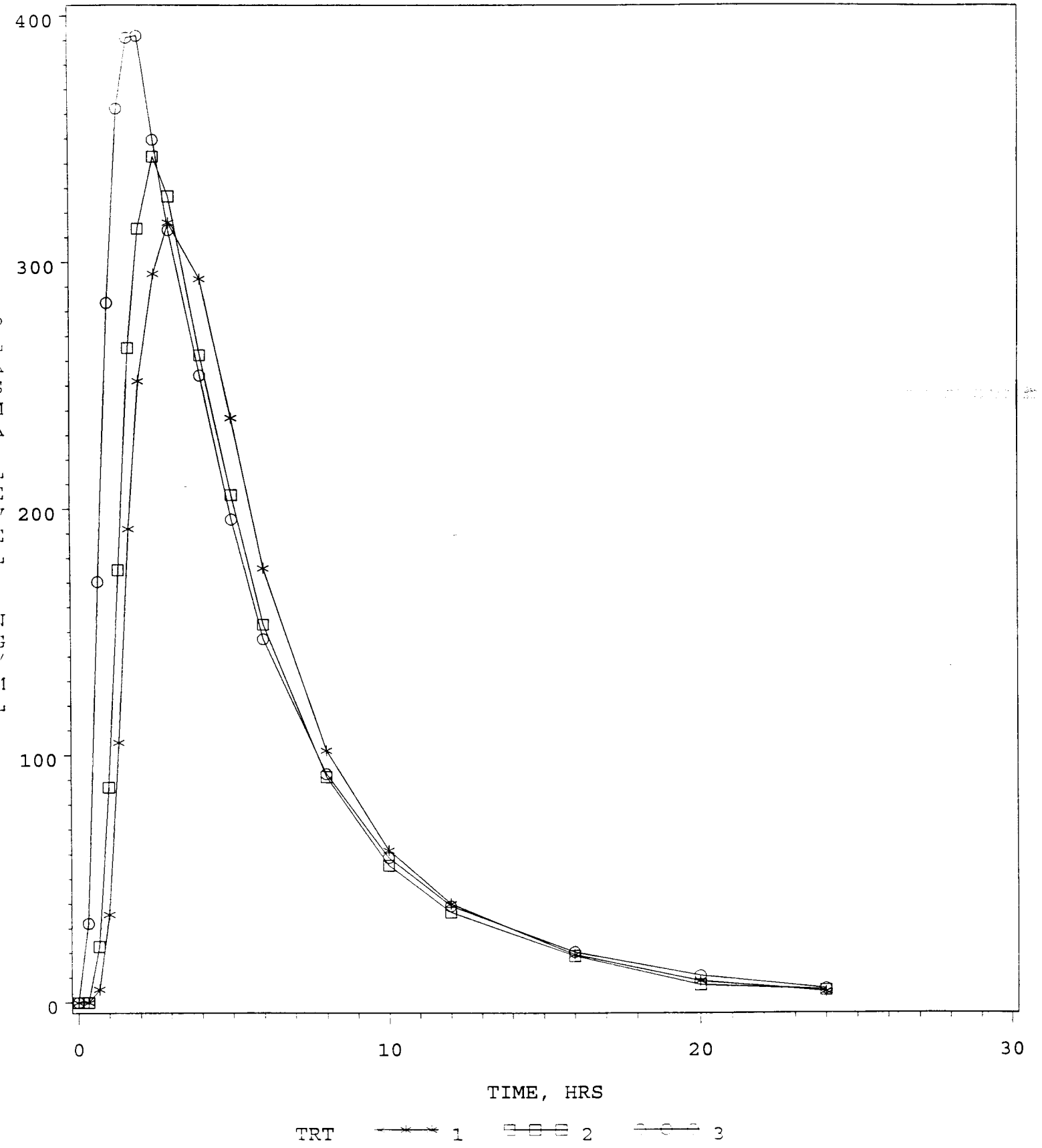
Attachment - 4

Attachment - 5

FIG P–2. ACYCLOVIR CAPSULES: PLASMA LEVELS

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-872
UNDER NON-FASTING CONDITIONS
DOSE=1 X 200 MG



1=TEST FED (TEST-LEDERLE) 2=REFERENCE FED (BURROUGHS-WELLCOME) 3=TEST FASTING (TEST-LEDERLE)

Table 5

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations for Acyclovir 200 mg Capsule (ESI Lederle, fed)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1											
2											
3											
4											
5											
6											
7											
8											
9											
11											
12											
13											
14											
15											
16											
18											
19											
20											
21											
Mean			361.2	2.83	1944.3	2030.7	0.1699	4.44	5.854	7.537	7.581
S.D.			105.7	0.83	583.0	598.1	0.0487	1.41	0.264	0.265	0.261
C.V.(%)			29.3	29.15	30.0	29.5	28.6729	31.66	4.516	3.516	3.447
S.E.M.			24.2	0.19	133.7	137.2	0.0112	0.32	0.061	0.061	0.060
N			19.0	19.00	19.0	19.0	19.0000	19.00	19.000	19.000	19.000
Minimum			245.7	1.67	1290.1	1390.0	0.0939	2.58	5.504	7.163	7.237
Maximum			621.9	5.00	3597.5	3694.6	0.2683	7.38	6.433	8.188	8.215

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Attachment - 6

Table 6

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Zovirax(R) 200 mg Capsule (Burroughs Wellcome Co.)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1											
2											
3											
4											
5											
6											
7											
8											
9											
11											
12											
13											
14											
15											
16											
18											
19											
20											
21											
Mean			375.4	2.49	1926.7	2025.4	0.1628	4.82	5.901	7.527	7.578
S.D.			87.6	0.82	515.8	536.7	0.0611	1.67	0.244	0.285	0.282
C.V.(%)			23.3	32.86	26.8	26.5	37.5094	34.58	4.132	3.786	3.715
S.E.M.			20.1	0.19	118.3	123.1	0.0140	0.38	0.056	0.065	0.065
N			19.0	19.00	19.0	19.0	19.0000	19.00	19.000	19.000	19.000
Minimum			200.1	1.00	949.4	990.6	0.0890	2.32	5.299	6.856	6.898
Maximum			539.8	5.00	2959.7	3072.6	0.2987	7.79	6.291	7.993	8.030

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Attachment - 7

Wyeth-Ayerst Laboratories
Acyclovir Protocol 95-099-MA
Harris Laboratories Project 17961

Table 7

Individual and Mean Pharmacokinetic Parameter Values From Serum Acyclovir Concentrations
for Acyclovir 200 mg Capsule (ESI Lederle, fasting)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1											
2											
3											
4											
5											
6											
7											
8											
9											
11											
12											
13											
14											
15											
16											
18											
19											
20											
21											
Mean			432.2	1.80	2194.2	2377.9	0.1582	5.05	5.928	7.570	7.680
S.D.			206.3	0.85	1123.8	1089.1	0.0586	2.08	0.611	0.521	0.445
C.V.(%)			47.7	47.42	51.2	45.8	37.0574	41.17	10.310	6.880	5.796
S.E.M.			47.3	0.20	257.8	256.7	0.0138	0.49	0.140	0.119	0.105
N			19.0	19.00	19.0	18.0	18.0000	18.00	19.000	19.000	18.000
Minimum			61.9	0.67	700.5	1009.0	0.0690	2.40	4.126	6.552	6.917
Maximum			857.1	4.00	4697.4	4789.3	0.2883	10.05	6.754	8.455	8.474

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Attachment 8